Original article
Korean J Pediatr 2017;60(1):10-16
https://doi.org/10.3345/kjp.2017.60.1.10
pISSN 1738-1061•eISSN 2092-7258

Korean J Pediatr

The influencing factors on procalcitonin values in newborns with noninfectious conditions during the first week of life

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Purpose: Although procalcitonin (PCT) level is useful for the diagnosis of neonatal sepsis, PCT reliability is inconsistent because of the varied conditions encountered in neonatal intensive care units. This study aimed to investigate PCT levels and factors influencing increased PCT levelin newborns without bacterial infection during the first week of life.
Methods: In newborns hospitalized between March 2013 and October 2015, PCT levels were measured on the first, third, and seventh days after birth. Newborns with proven bacterial (blood culture positive for bacteria) or suspicious infection (presence of C-reactive protein expression or leukocytosis/leukopenia) were excluded. Various neonatal conditions were analyzed to identify the factors influencing increased PCT level.
Results: Among 292 newborns with a gestational age of 35.2±3.0 weeks and a birth weight of 2,428±643 g, preterm newborns (n=212) had higher PCT levels than term newborns (n=80). Of the newborns, 7.9% had increased PCT level (23 of 292) on the firstday; 28.3% (81 of 286), on the third day; and 3.3% (7 of 121), on the seventh day after birth. The increased PCT level was significantly associated with prenatal disuse of antibiotics (P=0.004) and surfactant administration (P<0.001) on the first day after birth, postnatal use of antibiotics (P=0.001) and ventilator application (P=0.001) on the third day after birth, and very low birth weight (P=0.042) on the seventh day after birth.
Conclusion: In newborns without bacterial infection, increased PCT level was significantly associated with lower gestational age and respiratory difficulty during the first week of life. Further studies are needed for clinical applications.

Key words: Newborn infant, Procalcitonin, Premature birth, Dyspnea

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Received: 6 September, 2016
Revised: 6 October, 2016
Accepted: 18 October, 2016

Introduction

In neonates, bacterial infection is a frequent and important cause of neonatal mortality[1]. Therefore, it is important to diagnosis and treat bacterial infection early. White blood cell counts (WBC), C-reactive protein (CRP), cytokines, andcultures are usually used as diagnostic markers of bacterial infections. However, the existing diagnostic methods for infection have some weak points, namely diagnostic delays (for example, culture methods), suboptimal sensitivity (for example, blood cultures) and low specificity due to contamination (for example, sputum cultures).

Procalcitonin (PCT) is a diagnostic marker for severe bacterial infection and sepsis. PCT is a 116 amino acid peptide with an approximate molecular weight of 14.5 kDa[2]. It is secreted ubiquitously in response to endotoxin or mediators released through bacterial infections and strongly correlates with the severity of bacterial infections[3]. PCT has ashort half-life

and is known to be a specific marker for bacterial infections[4]. Even in neonates, sepsis or a systemic inflammatory reaction should always be considered if other causes cannot explain elevated PCT levels beyond a threshold level of 0.5 ng/mL[5].

Unspecific elevation of PCT levels in the absence of a bacterial infection may be possible in situations of massive stress, for example after severe trauma and surgery or patients that experience cardiac shock[6-9]. It must be noted that newborns generally have a physiological induction of inflammation in the first few days after birth[5,10,11].

Although PCT is helpful for the diagnosis of neonatal sepsis, there are discrepant results regarding PCT reliability because of variable conditions in neonatal intensive care units. Moreover, there are few reports about the conditions that influence PCT value in the neonatal period. The purpose of our study is to investigate the factors that increase PCT level other than bacterial infections.

Materials and methods

We retrospectively reviewed patients' medical records at Korea University Anam Hospital. A total of 292 neonates, who were born in our hospital or transferred from local hospitals within 72 hours after birth between March 2013 and October 2015, were enrolled. Newborns with confirmed bacterial infection (positive blood culture) or suspicious infection (positive CRP or leukocytosis/leukopenia) were excluded.

PCT values were measured on the1st, 3rd, and 7th days after birth. The PCT cutoff value was over 0.5 ng/mL on the 1st and 7th days and over 2 ng/mL on the 3rd day as the PCT level increased[12]. Serum PCT level was measured by electrochemiluminescent immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

We compared the PCT level of preterm infants with those of term infants within 1 week after birth to determine whether PCT level can be influenced by gestational age. Neonates were categorized into a normal PCT group and an increased PCT group. Various neonatal conditions were then analyzed to identify significant differences between the 2 groups. These conditions were perinatal chatacteristics such as gestational age, birth weight, sex, preterm infant, low birth weight, very low birth weight (VLBW), cesarian section, Apgar score, premature rupture of membrane, chorioamnionitis, maternal diabetes mellitus, prenatal antibiotics use, and neonatal conditions such as surfactant administration, meconium staining, application of a ventilator (invasive and noninvasive), patent ductus arteriosus (PDA), CRP, and WBC. We used multivariate logistic regression to exclude the possibility that several factors influence each other and to identify themore significant factors that influence PCT level.

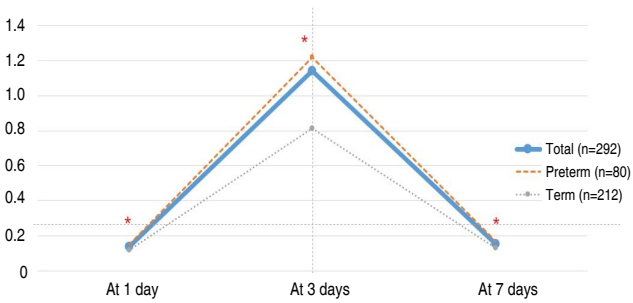
We categorized the infants as preterm when the gestational age was below 37. Premature rupture of the membrane was defined when the membrane ruptured over 18 hours before labor. PDA was defined when it was detected within 7 days after birth by echocardiogram. Chorioamninitis was defined when it was confirmed by placenta biopsy. Need of ventilator support refers to the use of a mechanical ventilator by the neonate within 1 week after birth. The neonates were included in the invasive ventilator group when they were intubated for mechanical ventilation. Noninvasive ventilator support included continuous positive airway pressure and high-flow nasal cannula.

Data processing and analysis were performed with IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). For categorical variables, the chi-square test and Fisher exact tests were used while theindependent *t*-test and Mann-Whitney test were used for continuous variables. We used multivariate logistic regression to identify the significant factors that influence PCT level. A value of $P<0.05$ was considered statistically significant.

Results

1. Subjects

A total of 292 neonates was enrolled in this study. The mean gestational age of the study population was 35.3±3.0 weeks and the mean birth weight was 2,428±643 g. Two hundred twelve neonates were categorized as preterm infants (gestational age<37 weeks) and 80 neonates were categorized as term infants (gestational age≥37 weeks). PCT assays were performed immediately after birth for all neonates. The assays were repeated at 48 hours (on 2nd day) after birth for 286 neonates and at 168 hours (on 7th day) after birth for 121 neonates.



Total	0.14 (0.11-0.23)	1.14 (0.48-2.30)	0.16 (0.12-0.22)
Preterm	0.15 (0.11-0.23)	1.22 (0.55-2.56)	0.17 (0.13-0.25)
Term	0.12 (0.09-0.21)	0.82 (0.43-1.84)	0.13 (0.11-0.16)

*$P<0.05$ between preterm and term groups.
Values expressed as median (25th-75th percentile).

Fig. 1. Comparison of the procalcitonin levels of the preterm and term infants within 1 week after birth.

2. Comparison of PCT levels between preterm and term infants in 1st week

The mean PCT level on the 1st day after birth was 0.14 ng/mL (292 neonates) and the value on the 3rd day was 1.14 ng/mL (286 neonates). The mean PCT level on the 7th day after birth was 0.155 ng/mL (121 neonates). There were significant differences in PCT levels between term and preterm neonates on the 1st, 3rd, and 7th days after birth (Fig. 1).

3. Influencing factors of increased PCT level without infection

The PCT level on the1st day after birth showed a statistically significant difference according to gestational age, VLBW, very low Apgar score at 5 minutes (<4), prenatal antibiotics use and surfactant administration (Table 1). By multivariate binary logistic regression analysis, the most significant factors for increased PCT level on the 1st day were prenatal antibiotic use, surfactant administration, CRP onthe 1st day (Table 2).

The PCT level on the 3rd day after birth showed statistically significant differences in gestational age, surfactant administration, application of ventilator, application of noninvasive ventilator and postnatal antibiotics use (Table 3). According to multivariate binary logistic regression analysis, the most significant factors for increased PCT level on the 3rd day after birth were ventilator application, postnatal antibiotic use, and CRP on the

Table 1. Comparison of factors that can influence procalcitonin level in the normal group (≤0.5 ng/mL) and the group (>0.5 ng/mL) with increased procalcitonin levelon the first day after birth

Variable	Normal group (n=269)	Increased group (n=23)	*P* value
Gestational age (wk)	35.2±2.8	35.0±5.1	NS
Birth weight (g)	2,424±614	2,483±942	NS
Male sex	146 (54.3)	16 (69.6)	NS
Preterm (<37 wk)	201 (74.7)	11 (47.8)	0.006
LBW	158 (58.7)	9 (39.1)	NS
VLBW	17 (6.3)	4 (17.4)	0.049
Cesarean section	170 (63.2)	13 (56.5)	NS
Low AS at 1 min (<7)	76 (28.4)	6 (26.1)	NS
Very low AS at 1 min (<4)	17 (6.3)	1 (4.3)	NS
Low AS at 5 min (<7)	22 (8.2)	2 (8.7)	NS
Very low AS at 5 min (<4)	0 (0)	1 (4.3)	0.001
PROM	89 (33.1)	6 (26.1)	NS
Chorioamnionitis	18 (6.7)	2 (9.1)	NS
Maternal DM	32 (11.9)	0 (0)	NS
Prenatal antibiotics	181 (67.5)	7 (33.3)	0.002
Surfactant administration	19 (7.1)	5 (21.7)	0.014
Meconium stained	8 (3.0)	1 (4.3)	NS
Ventilator application	95 (35.3)	10 (43.5)	NS
C-reactive protein (mg/L)	0.11 (0.08–0.15)	0.70 (0.26–1.49)	<0.001
White blood cell (/μL)	10,000 (7,860–12,840)	19,800 (14,100–22,900)	<0.001

Values are presented as mean±standard deviation, number (%), median (25th–75th interquartile).
LBW, low birth weight defined as birth weight <2,500 g; VLBW, very low birth weight defined as birth weight <1,500 g; AS, Apgar score; PROM, premature rupture of membrane; DM, diabetes mellitus; CRP, C-reactive protein; WBC, white blood cell; NS, not significant (*P*≥0.05)

Table 2. Multivariate binary logistic regression analysis of factors that can influence procalcitonin level on the first day after birth

Variable	Crude OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
Preterm (GA<37 wk)	0.31 (0.13–0.74)	0.008	0.84 (0.153–4.658)	NS
VLBW (<1,500 g)	3.12 (0.95–10.21)	NS	0.25 (0.02–2.57)	NS
Prenatal antibiotics	0.24 (0.09–0.62)	0.003	0.08 (0.01–0.51)	0.008
Surfactant administration	3.66 (1.22–10.93)	0.020	39.27 (5.17–298.20)	<0.001
C-reactive protein	201.53 (26.96–1506.76)	<0.001	266.82 (24.83–2867.56)	<0.001
White blood cell	6.961 (3.30–14.67)	<0.001	2.579 (0.94–7.07)	NS

OR, odds ratio; CI, confidence interval; GA, gestational age; VLBW, very low birth weight; NS, not significant (*P*≥0.05).
*aOR: adjusted for preterm birth, VLBW, prenatal antibiotics, surfactant administration, serum C-reactive protein level, and white blood cell count.

 https://doi.org/10.3345/kjp.2017.60.1.10

Table 3. Comparison of several factors that can influence procalcitonin level in the normal group (≤2 ng/mL) and the group (>2 ng/mL) with increased procalcitonin level on the third day after birth

Variable	Normal group (n=205)	Increased group (n=81)	*P* value
Gestational age (wk)	35.4±2.9	34.4±3.1	0.009
Birth weight (g)	2,452.2±628.6	2,356.7±656.2	NS
Male sex	105 (51.2)	52 (64.2)	0.047
Preterm (GA<37 wk)	145 (70.7)	66 (81.5)	NS
LBW (BW<2,500 g)	120 (58.5)	45 (55.6)	NS
VLBW (BW<1,500 g)	11 (5.4)	9 (11.1)	NS
Cesarean section	106 (59.2)	49 (68.1)	NS
Low AS at 1 min (<7)	58 (28.3)	22 (27.5)	NS
Very low AS at 1 min (<3)	12 (5.9)	5 (6.2)	NS
Low AS at 5 min (<7)	13 (6.3)	10 (12.5)	NS
Very low AS at 5 min (<3)	0 (0.0)	1 (1.2)	NS
PROM	71 (34.6)	23 (28.4)	NS
Chorioamnionitis	13 (6.4)	7 (8.6)	NS
Maternal DM	23 (11.2)	9 (11.1)	NS
Prenatal antibiotics	131 (64.5)	56 (70)	NS
Surfactant administration	11 (5.4)	12 (14.8)	0.008
Meconium stained	9 (4.4)	0 (0)	NS
Ventilator application	55 (26.8)	49 (60.5)	<0.001
Invasive vent application	12 (5.9)	9 (11.1)	NS
Noninvasive vent application	50 (24.4)	43 (53.1)	<0.001
Patent ductus arteriosus	43 (21)	24 (29.6)	NS
Postnatal antibiotics	134 (65.4)	80 (98.8)	<0.001
C-reactive protein	0.59 (0.340–1.265)	0.86 (0.500–1.755)	0.003
White blood cell	11,200 (9,300–13,650)	11,900 (9,600–14,120)	NS

Values are presented as mean±standard deviation, number (%), median (25th–75th interquartile).
GA, gastrointestinal age; LBW, low birth weight defined as birth weight <2,500 g; VLBW, very low birth weight defined as birth weight <1,500 g; AS, Apgar score; PROM, premature rupture of membrane; DM, diabetes mellitus; NS, not significant (P≥0.05).

Table 4. Results of the multivariate binary logistic regression analysis of factors that can influence procalcitonin level on the third day after birth

Variable	Crude OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
Gestational age (wk)	0.983 (0.972–0.996)	0.007	0.990 (0.971–1.010)	NS
Male sex	0.586 (0.345–0.995)	0.048	0.638 (0.354–1.152)	NS
Surfactant administration	3.067 (1.294–7.270)	0.011	0.553 (0.134–2.287)	NS
Vent application	4.176 (2.428–7.182)	0.000	2.596 (1.464–4.605)	0.001
Noninvasive vent application	3.508 (2.043–6.022)	0.000	0.929 (0.185–4.675)	NS
Postnatal antibiotics	42.388 (5.777–311.039)	0.000	29.844 (4.011–222.040)	0.001
C-reactive protein	1.324 (1.060–1.653)	0.013	1.289 (1.012–1.640)	0.039

OR, odds ratio; CI, confidence interval; GA, gestational age; VLBW, very low birth weight; NS, not significant (P≥0.05).
*aOR: adjusted for preterm birth, VLBW, prenatal antibiotics, surfactant administration, serum C-reactive protein level, and white blood cell count.

3rd day (Table 4).

The PCT level on the 7th day after birth showed statistically significant differences in VLBW, very low apgar score at 1 minute, chorioamninitis, surfactant administration, invasive ventilator application, and PDA (Table 5). According to multivariate binary logistic regression analysis, the most significant factors for increased PCT level on the 7th day after birth were VLBW and invasive ventilator use (Table 6).

Discussion

PCT levels increased significantly on the 3rd day of birth compared to the 1st day and decreased on the 7th day of birth in

Table 5. Comparison of several factors that can influence procalcitonin level in the normal group (≤2) and the group (>2) with increased procalcitonin level on the seventh day after birth

Variable	Normal group (n=117)	Increased group (n=4)	*P* value
Gestational age (wk)	34.8±2.8	28.1±5.5	NS
Birth weight (g)	2,366.4±607.2	1,317.5±882.8	NS
Male sex	71 (60.7)	2 (50.0)	NS
Preterm (GA<37 wk)	93 (79.5)	4 (100)	NS
LBW (BW<2,500 g)	70 (59.8)	3 (75.0)	NS
VLBW (BW<1,500 g)	7 (6.0)	3 (75.0)	<0.001
C/sec	78 (66.7)	3 (75.0)	NS
Low AS at 1 min (<7)	40 (34.5)	2 (50.0)	NS
Very low AS at 1 min (<3)	6 (5.2)	2 (50.0)	<0.001
Low AS at 5 min (<7)	9 (7.8)	3 (75.0)	<0.001
Very low AS at 5 min (<3)	0 (0)	1 (25.0)	<0.001
PROM	37 (31.6)	2 (50.0)	NS
Chorioamnionitis	8 (6.8)	2 (50.0)	0.002
Maternal DM	12 (10.3)	0 (0)	NS
Prenatal antibiotics	84 (72.4)	4 (100)	NS
Surfactant administration	11 (9.4)	3 (75.0)	<0.001
Meconium stained	3 (2.6)	0 (0)	NS
Ventilator application	60 (51.3)	4 (100)	NS
Invasive vent application	8 (6.8)	3 (75.0)	<0.001
Noninvasive vent application	56 (47.9)	2 (50.0)	NS
Postnatal antibiotics	30 (25.6)	3 (75.0)	0.029
Postnatal antibiotics	109 (93.2)	3 (75.0)	NS
C-reactive protein (mg/L)	0.250 (0.180–0.420)	0.175 (0.093–0.468]	NS
White blood cell (unit)	11,700 (9,510–13,400)	14,050 (9,860–23,700]	NS

Values are presented as mean±standard deviation, number (%), median (25th–75th interquartile).
BW, birth weight; LBW, low BW defined as BW<2,500 g; VLBW, very low BW defined as BW <1,500 g; AS, Apgar score; PROM, premature rupture of membrane; DM, diabetes mellitus; NS, not significant (*P*≥0.05).

Table 6. Results of the multivariate binary logistic regression analysis of factors that can influence procalcitonin level on the seventh day after birth

Variable	Crude OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
VLBW	78.571 (8.045–767.344)	0.000	17.130 (1.104–265.852)	0.042
Chorioamnionitis	13.625 (2.358–78.718)	0.004	7.458 (0.458–121.396)	NS
Surfactant administration	48.182 (5.155–450.329)	0.001	2.272 (0.006–797.550)	NS
Invasive-vent application	68.125 (7.081–655.389)	0.000	13.430 (0.860–209.603)	NS
Patent ductus arteriosus	14.500 (1.628–129.143)	0.017	0.600 (0.002–220.724)	NS
Postnatal antibiotics	42.388 (5.777–311.039)	0.000	29.844 (4.011–222.040)	0.001

aOR: adjusted for VLBW, chorioamnionitis, surfactant administration, invasive-vent application, patent ductus arteriosus.
OR, odds ratio; CI, confidence interval; VLBW, very low birth weight defined as birth weight <1,500 g; NS, not significant (*P*≥0.05).

our study. This result was observed regardless of preterm or term infants. Assumma et al.[11] reported a physiological surge of PCT levelsinneonates in the first 2 days after birth. This seems to be due to the reaction to birth with nonspecific activation of the immune system[13].

Previous studies reported that PCT level is lower in premature infants because of an immature immune system[10,14]. In another study by Chiesa et al.[5], prematurity did not affect PCT levels. However, in our study, PCT levels were significantly higher in preterm infants on the 1st, 3rd, and 7th days after birth. According to logistic regression analysis, gestational age was not a significant influencing factor in increasing PCT levels. The effect of respiratory difficulty on the PCT level is not excluded because more preterm infants showed respiratory difficulty in the early period after birth. In our study, respiratory difficulty, which was represented by surfactant administration and ventilator appli-

cation, also affected the increased PCT level. There were 19 term infants (23.8%) and 86 preterm infants (40.6%) who showed respiratory difficulty (P=0.005). The effect of respiratory difficulty on the increased PCT level was already reported in previous studies[8,15]. The increased PCT levelson the 1st and 3rd days after birth seem to be mainly due to respiratory difficulties in infants but may also be affected by noninfectious inflammatory responses. Further studies will be needed to confirm the pathophysiology.

In VLBW infants, PCT levels increased without infection especially on the 7th day after birth. This point should be considered to interpret the response to treatment for suspicious infections and may be useful to reduce antibiotics use within the 1st week after birth.

In the prenatal antibiotics use group, PCT level was lower than that in the prenatal antibiotics disuse group. Chiesa et al.[5] reported that the use of prenatal antibiotics could be related to false-negative PCT levels inneonates with early-onset sepsis. Prenatal antibiotics disuse was a significantly influencing factor on increased PCT levels although infants confirmed to have suspicious infections by other diagnostic markers were excluded in our study. We assume that there are other causes for neonatal infection besides false-negative results, for example, controlled infection by prenatal antibiotics use.

On the other hand, postnatal antibiotic use was an influencing factor on increased PCT level. Postnatal antibiotics was administered when infants had deteriorative conditions such as respiratoy symptoms, maternal infections, and so on. Infants with increased CRP levels were excluded from our study, however, CRP level within normal range was also significantly correlated with PCT level. Therefore, some inflammatory reactions such as these infection-likely conditions would influence the PCT level of infants.

There are some limitations in our study. First is that it was a retrospective study. Even though 292 neonates were enrolled in the study, the number of PCT assays performed for each infant within the first week after birth varied. The PCT level on the 1st day of birth was routinely checked in all neonates, but the PCT levels on the 3rd and 7th days were checked depending on the infant's condition and some neonates were discharged before the 7th day after birth. So, the number of infants that received PCT assays on the 7th day after birth was small (121 cases), and especially, only 4 infants had increased PCT levels on the 7th day. This limited the validity of our study. Another limitation is that the possibility of nonbacterial infections could not be eliminated. Although we excluded cases of suspicious infection confirmed by increased biomarkers, viral or fungal infections cannot be confirmed in this manner. However, in our study, the PCT levels of the infants were checked serially within the 1st week after birth to identify noninfectious conditions that could increase PCT levels, unlike previous studies.

PCT concentration can increase physiologically during the first few days of life, which interfere with the interpretation of the PCT level[16]. Different hourly cutoff values for the PCT level were introduced to address this issue, but the reliability of PCT level for neonatal sepsis is still controversial[17]. The increased PCT level is also possible in several perinatal conditions, such as respiratory distress syndrome, inhalation injury, hemodynamic failure and asphyxia[17]. The interpretation of PCT levels for diagnosing infection maybe influenced by several factors. Hence, it is helpful to determine the influencing factors for clinical application of PCT level in neonates.

In conclusion, PCT is a useful diagnostic marker for neonatal sepsis, but the PCT levels of neonates should be interpreted by taking into account various noninfectious factors such as time after birth, gestational age, and respiratory difficulty. We recommend the interpretation of neonate PCT levels with consideration of these factors.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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